63. (New) The method of Claim 58, 59, or 60 wherein said erythropoietin is native erythropoietin, recombinant human erythropoietin or animal erythropoietin or a derivative thereof.

REMARKS

At the outset, applicants thank Examiners DeBerry and Kemmerer for the courtesies extended during the telephonic interview of December 12, 2002 with Dr. Anthony Cerami, one of the inventors of the above-captioned application, Frederick J. Hamble, Esq. of The Kenneth S. Warren Laboratories, Inc., and Applicants' representatives Laura A. Coruzzi and Eileen E. Falvey of Pennie & Edmonds, LLP. The amendments and remarks made herein are in response to the Office Action mailed October 22, 2002 and reflect the content of the discussion and suggestions made by the Examiners during that interview.

Claims 28-39 are pending in the instant application. By this amendment, claim 34 has been amended and new claims 40-63 have been added to clarify the invention and place the claims in condition for allowance. No new matter is added by this amendment, which is fully supported by the specification and claims as originally filed (for example, see p. 13, *ll.* 24-26 and p. 22, *l.* 32 to p. 23, *l.* 20).

1. THE REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, SHOULD BE WITHDRAWN

Claims 28-39 are rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. The Examiner contends that the claimed method for treating cerebral ischemia using non-toxic amounts of erythropoietin would require undue experimentation. This rejection is in error and should be withdrawn for the reasons detailed below.

Applicants submit that the claimed method is fully described and enabled by the teachings of the specification as it would be understood and applied by one skilled in the art. For example, the specification describes formulations and non-toxic dosages of erythropoietin that could be used to achieve neuroprotection (specification at p. 22, *l.* 25 to p. 24, *l.* 6; see also p.4, *ll.* 26-27). The instant specification also enumerates the factors that should be considered to determine appropriate non-toxic dosage of erythropoietin, and specifies that the

skilled practitioner should readily be able to make such a determination according to standard clinical techniques. For example, p. 22, *l.* 32 to p. 23, *l.* 9 states:

> Selection of the preferred effective dose will be determined by a skilled artisan based upon considering several factors which will be known to one of ordinary skill in the art. Such factors include the particular form of erythropoietin, and its pharmacokinetic parameters such as bioavailability, metabolism, half-life, etc., which will have been established during the usual development procedures typically employed in obtaining regulatory approval for a pharmaceutical compound further factors in considering the dose include the condition or disease to be treated or the benefit to be achieved in a normal individual, the body mass of the patient, the route of administration, whether administration is acute or chronic, concomitant medications, and other factors well known to affect the efficacy of administered pharmaceutical agents. Thus the precise dosage should be decided according to the judgment of the practitioner and each patient's circumstances, *e.g.*, depending upon the condition and the immune status of the individual patient, according to standard clinical techniques.

Given this direction, the skilled practitioner would be able to make appropriate determinations and choices using ordinary skill. In this regard, the Examiner's attention is invited to the 2000 edition of the Physicians' Desk Reference ("PDR"), the art-accepted standard reference manual for practitioners at the relevant time; and, in particular, the section of the PDR relating to erythropoietin (see PDR, pp. 519-525 and 2125-2131, a copy of which is provided herewith as Exhibit C). The PDR shows that, depending on the patient population being treated with erythropoietin, different hematocrit ranges are targeted to avoid toxicity.[1] The PDR shows that practitioners monitor the patient's hematocrit during therapy

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[1] For example, in patients with chronic renal failure, the PDR recommends dosing erythropoietin to achieve non-toxic target hematocrits ranging from 30% to 36% (*e.g.*, see PDR, p. 523, col. 1, *ll.* 17-96 and p. 2129, col. 1, *ll.* 8-93, and accompanying table in cols. 2 and 3). The PDR notes that toxicity in the form of polycythemia (a condition marked by an abnormal increase in the number of circulating red blood cells) can be avoided by carefully monitoring the hematocrit and adjusting doses of EPO, withholding erythropoietin if the hematocrit approaches the high-end of the target range (36% for this patient population) or increases by more than 4 points in any 2-week period, until the hematocrit returns to the

(continued...)

with erythropoietin and, to avoid toxicity, adjust the dose and/or withhold treatment if the patient's hematocrit approaches or exceeds the upper limits of a target range. Therefore, the skilled practitioner, armed with the teachings of the instant specification, would be able to administer doses of erythropoietin sufficient to achieve neuroprotective effects, yet avoid toxic side effects, *e.g.*, simply by monitoring the patient's hematocrit and adjusting the dosing of erythropoietin to maintain the patient's hematocrit within the desired target range. Thus, the teachings of the instant application can be successfully practiced without undue experimentation, and the claims are enabled.

In view of the foregoing, applicants submit that the rejection for lack of enablement under 35 U.S.C. § 112, first paragraph, is in error and should be withdrawn.

2. THE REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH, SHOULD BE WITHDRAWN

Claim 32 is rejected under 35 U.S.C. § 112, second paragraph, for indefiniteness, as being ambiguous. The applicants submit that, for the reasons discussed in Section 1 above, the metes and bounds the term "a non-toxic amount of erythropoietin" is readily determined by the skilled artisan. As such, applicants submit that the rejection for indefiniteness under 35 U.S.C. § 112, second paragraph, has been overcome and request its withdrawal.

3. MISCELLANEOUS MATTERS

Applicants take this opportunity to bring to the attention of the Examiner the reference Albayrak *et al.*, 1997, ACTA Neuropathol. 94: 158-163 ("Albayrak"), a copy of which is provided herewith as Exhibit D. Applicants believe Albayrak supports the patentability of the instantly claimed invention, and is merely cumulative to information already of record in the

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[1](...continued)
suggested target range (30% to 36% for this patient population; see PDR, p. 523, col. 1, and p. 2129, col. 1, under "Dose Adjustment"). In contrast, for cancer patients on chemotherapy, the PDR teaches to adjust the dosage at a different hematocrit level, *i.e.*, if the hematocrit exceeds 40% (see p. 2129, col. 2, under "Dose Adjustment").

instant application, and therefore is not material to patentability under Rule 1.56(b). Although Albayrak has not been cited in connection with any of the applicants' counterpart foreign applications, we take this opportunity to note that Albayrak was cited by the European Patent Office in connection with the European examination of WO 00/35475 (Ref. AR of record). Applicants note that reference AR designates the United States, and according to the USPTO records, entered the national stage on June 28, 2001 as U.S. Application No. 09/868,089.

CONCLUSIONS

Applicants respectfully request that the foregoing amendments and remarks be made of record in the file history of the instant application. Applicants estimate that the remarks and amendments made herein now place the pending claims in condition for allowance.

Respectfully submitted,

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Enclosures